

## II. INTERVIEWS

### A. Substance of the telephonic interview of April 13, 2005

In a telephonic interview on April 13, 2005, between Examiner Gary Nickol, Ph.D., of the USPTO, and Charles Rories, Ph.D. (Reg. No. 43,381) of the undersigned's law firm, representing the applicants, the examiner stated that an advisory action would be issued because the chemical descriptions of the trademarked compounds specified in the claims are allegedly new matter. Referring to the chemical descriptions of the Pluronic® and Tetronic® block polymers to which claims 53 and 57 refer, Dr. Rories stated that the chemical descriptions of these compounds were well known at the time of filing, as described in the Schmolka (1977) and Hunter et al. (1981) references that are cited and incorporated by reference in the present application (see page 10). Dr. Rories proposed submitting a supplemental amendment that amends the specification and claims by adding the chemical descriptions of these compounds as described in the Schmolka (1977) and Hunter et al. (1981) references. The examiner agreed to consider such a supplemental amendment, and advised that a signed affidavit must be submitted with the supplemental amendment that declares that the added subject matter is the same as that described by the cited references. The examiner further advised that disposition of the application will depend on the results of any further searches of prior art that are performed.

### B. Substance of the telephonic interview of April 28, 2005

In an additional telephonic interview on April 28, 2005, Examiner Gary Nickol and Charles Rories, Ph.D. discussed scheduling a telephonic interview on May 3, 2005, that would include the undersigned, representing the applicants, in order to discuss whether amending page 11 of the specification and claims 53 and 62 to include chemical descriptions of the specified trademarked detergents that were well-known by persons in the art at the time of filing would constitute new matter. The examiner agreed to an additional telephonic interview on May 3, 2005, and suggested that the opinion of a USPTO official associated with Patent Quality Assurance be obtained on this question, and provided contact information for Ms. Diana Dudash of the USPTO.

C. Substance of the telephonic interview of April 29, 2005

In a telephonic interview on April 29, 2005, Dr. Rories requested of Ms. Diana Dudash (USPTO Patent Quality Assurance) if it is possible to amend the specification and related claims of an application by inserting a well-known chemical description of a trademarked product into the specification and related claims, and submitting evidence with the amendment that the chemical description of the trademarked product inserted by the amendment was well-known by persons skilled in the art at the time of filing, without the amendment being rejected for the addition of new matter. Ms. Dudash responded that such an amendment sounded "reasonable," but that the decision to allow such an amendment must be made at the Art Unit level by either the examiner or the Art Unit SPE.

D. Substance of the telephonic interview of May 3, 2005

In a telephonic interview on May 3, 2005, with Examiner Gary Nickol, and Dr. Charles Rories, the undersigned summarized the above-identified discussion between Ms. Dudash and Dr. Rories, and proposed that a supplemental amendment be submitted that amends the specification and claims 53 and 62 by inserting the well-known chemical descriptions of the trademarked detergents, PEG1000 and Pluronic® L121 (poloxamer 401). The undersigned stated that the proposed amendment would cancel claim 57 because amendment to include chemical descriptions of all of the Pluronic® and Tetronic® block polymers specified in claim 57 would be cumbersome and a burden for the examiner to review. The undersigned further stated that the following would be submitted with the proposed amendment: (a) evidence that the added chemical descriptions of the trademarked detergents, PEG1000, and Pluronic® L121 were well-known by persons skilled in the art at the time of filing; (b) a signed affidavit (enclosed herewith) that declares that chemical descriptions added to the specification and claims were well-known by persons skilled in the art, are identical to the descriptions given in the cited publications, and do not constitute new matter, and (c) summaries of the telephonic interviews of April 13, 2005, April 28, 2005, April 29, 2005, and May 3, 2005. The examiner agreed to consider the proposed supplemental amendment and accompanying submissions.

### III. REMARKS

#### PRELIMINARY REMARKS

##### Amendment of the specification

(1) The paragraph beginning on page 11, line 4, of the specification is amended to include in parentheses the chemical names of the detergents that are identified by common or trademarked names in the specification. The chemical names of the specified detergents were well-known by persons skilled in the art at the time of filing.

The specification identifies TWEEN 80 as sorbitan-mono-9-octadecenoate-poly(oxy)-1,2-ethanediyl (see p. 11, line 6). At the time of filing, the chemical names of the related detergents TWEEN 20, TWEEN 40, and TWEEN 60 were well-known to be, respectively, polyoxyethylenesorbitan monolaurate, polyoxyethylenesorbitan monopalmitate, and polyoxyethylenesorbitan monostearate (for example, see Crispens et al., "Evaluation of the anticancer activities of Tweens 20, 40 and 60 in SJL/J mice," *Anticancer Res.*, 1991, 11(1):407-8; (abstract attached).

ZWITTERGENT 3-12 was well-known at the time of filing to be N-dodecyl-N,N-dimethyl-3-ammonio-1-propanesulfonate (e.g., see Miller et al., "The Purification and Characterization of the Cytochrome d Terminal Oxidase Complex of the Escherichia coli Aerobic Respiratory Chain," *J Biol. Chem.*, 1983, 258(15):9159-9165; see page 9159, right column at bottom, copy attached). The name ZWITTERGENT in the paragraph (p. 11, line 7) is re-written in capital letters, pursuant to M.P.E.P. §608.01(v).

TEEPOL HB7 was well-known at the time of filing to be alkyl (C9-C13) sodium sulfates (e.g., see column 10 of U.S. Patent No. 5,932,212, of Khalaf, which was filed May 24, 1996; copies of the first page and the page with column 10 are attached).

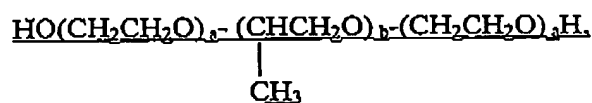
SPAN 85 was well-known at the time of filing to be sorbitan trioleate (e.g., see Blondino et al., "The quantitative determination of aspirin and its degradation products in a model solution aerosol," *J Pharm Biomed Anal.*, 1995, 13(2):111-9; abstract attached).

(2) The paragraph beginning on page 11, line 10, of the specification is amended to include chemical descriptions of PEG 1000 and the block polymer surfactant PLURONIC L121 (poloxamer 401).

At the time of filing, PEG 1000 was well-known to refer to polyethylene glycol having average molecular weight of 1000 (e.g., see Morris et al., "Structural properties of

polyethylene glycol-polysorbate 80 mixture, a solid dispersion vehicle," 1992, J Pharm Sci. 81(12):1185-8, abstract attached).

Chemical descriptions of block polymer surfactants such as PLURONIC L121 (poloxamer 401) are found in Schmolka ("A Review of Block Copolymer Surfactants," J. Am. Oil. Chem. Soc., 1977, 54:110; copy attached) and Hunter et al. ("The Adjuvant Activity of Nonionic Block Polymer Surfactants," J. Immunol., 1981, 127(3):1244; copy attached), both of which were cited in the present application (page 11, lines 15-16). The paragraph beginning on page 11, line 10, is amended to specify that the block polymer surfactants identified in the specification are called block polymers because they contain polyoxypropylene (POP) and polyoxyethylene (POE) portions which occur in separate blocks, as described on page 1245 of Hunter et al. (top of right column). The same paragraph is further amended to describe the chemical structure of the block co-polymer PLURONIC L121 (poloxamer 401) as having the general structure:  $(\text{POE})_a-(\text{POP})_b-(\text{POE})_a$ , as shown below:



wherein a and b are such that the average molecular weight of the polyoxypropylene blocks in the molecule is 4000, and approximately 10% of the molecular weight of the copolymer is composed of the polyoxyethylene blocks. This chemical description of PLURONIC L121 (poloxamer 401) is the same as that given in Figure 1 and in the bridging paragraph on page 110 of Schmolka, which describes the chemical structure of the poloxamer surfactants, and in Table 1 on page 112 of Schmolka, which describes the physical characteristics of poloxamer 401. The same description of the chemical structure and characteristics of PLURONIC L121 (poloxamer 401) is also given in Figure 1 on page 1245 of Hunter et al. (1981). A clerical error in the citation of the Hunter et al. (1981) reference on line 16 of page 11 that incorrectly identified the volume as vol. 129 instead of vol. 127(3) is also corrected by the amendment.

Amendment of the claims

Claims 44, 48, 52, 53, and 62-64 are amended, and claims 47 and 57 are canceled.

Claim 44 is amended to specify that the at least one TGF $\beta$ -neutralizing agent is selected from the group consisting of an anti- $\beta$  antibody, a TGF $\beta$ R-fusion protein, a TGF $\beta$  analog, a TGF $\beta$  binding protein, and a TGF $\beta$ R blocking antibody. This feature is incorporated from claim 47; accordingly, claim 47 is canceled, and claim 48 is amended to depend on claim 44 rather than on claim 47.

Claim 52 is amended to depend on claim 51.

Claims 53 and 62 are amended to refer to the specified compounds by their well-known chemical descriptions. As discussed below, claim 57 is canceled in the interest of expediting prosecution.

Claims 63 and 64 are amended to specify that the immunostimulating peptide to which the claims refer is muramyl dipeptide, as described, on page 12, lines 11-14.

PATENTABILITY REMARKSObjections

The official action objected to claim 52 as being ambiguous because it depended on itself. The dependence of claim 52 on itself was a typographic error, which has been corrected by amending claim 52 to depend on claim 51.

35 U.S.C. §112, Second Paragraph

Claims 53, 57, and 62 were rejected under 35 U.S.C. §112, second paragraph, because they contain references to trademarked product names. Claims 53 and 62 are amended to refer to the specified detergents, to PEG 1000, and to poloxamer 401 block polymer, by their chemical descriptions, which were well-known by persons of skill in the art at the time of filing, as discussed above.

The Pluronic<sup>®</sup> and Tetronic<sup>®</sup> surfactants specified in claim 57 were well-known at the time of filing; for example, see, Schmolka, J. Am. Oil. Chem. Soc., 54:110 (1977) and Hunter et al., J. Immunol., 129:1244 (1981), copies of which are attached. As can be seen from the form of the chemical description of PLURONIC L121 (poloxamer 401) which is added by amendment to the specification and to claim 62, as described above, chemical descriptions of the specified examples of Pluronic<sup>®</sup> and Tetronic<sup>®</sup> surfactants of the disclosed invention are lengthy and complex. Amendment of the specification and claims to include chemical descriptions of each of the specified Pluronic<sup>®</sup> and Tetronic<sup>®</sup> surfactants specified in claim 57

would involve extensive revision of the specification and claims, which would then would require significant review by the examiner. Accordingly, in the interest of expediting prosecution, claim 57 is canceled.

In view of the foregoing, withdrawal of the rejection of claims 53, 57, and 62 under 35 U.S.C. §112, second paragraph, is respectfully requested.

35 U.S.C. §112, First Paragraph

Claims 63-64 were rejected under 35 U.S.C. §112, first paragraph, because the specification is considered to lack written description of the invention of claims 63 and 64 except wherein the immunostimulating peptide is muramyl dipeptide. Claims 63-64 have been amended to specify that the immunostimulating peptide is muramyl dipeptide, and withdrawal of the rejection under 35 U.S.C. §112, First Paragraph, is respectfully requested.

35 U.S.C. § 103(a)

Claims 44-46 and 49-64 were rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable in view of Raychaudhuri et al. (U.S. Patent No. 5,695,770), in combination with Berd et al. (U.S. Patent Application No. 2002/0004052) and Berd et al. (Cancer Research, Vol. 46, May 1986, pp. 2572-7), for the reasons of record.

Claims 47-48 were objected to as being dependent upon a rejected base claim, but would be considered allowable if re-written in independent form, including all of the limitations of the base claim and any intervening claims.

Claim 44 has been amended to incorporate from claim 47 the feature that the at least one TGF $\beta$ -neutralizing agent is selected from the group consisting of an anti-TGF $\beta$  antibody, a TGF $\beta$ R-fusion protein, a TGF $\beta$  analog, a TGF $\beta$  binding protein, and a TGF $\beta$ R blocking antibody. In addition, claim 47 is canceled, and claim 48 is amended to depend on claim 44 rather than on claim 47. Withdrawal of the rejection of claim 44-46 and 49-64 under 35 U.S.C. § 103(a), and the objection to claims 47 and 48, is respectfully requested.

#### IV. CONCLUSION

All rejections and objections having been addressed, it is respectfully submitted that the present application is in condition for allowance and a notice to that effect is earnestly solicited. If any points remain in issue, which the examiner feels may be best resolved through a personal or telephone interview, he is kindly requested to contact the undersigned attorney at the telephone number listed below.

Respectfully submitted,



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